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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,090	09/30/2005	Kurt Lang	20968	1980

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

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01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,090	LANG ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/11/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 11, 2009, has been entered.

2. The amendment filed December 11, 2009, is acknowledged and has been entered. Claims 18-21 have been canceled. Claims 22-24 have been newly added.

3. Claims 22-24 are pending and are under examination.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The rejection of claims 22-24 under 35 U.S.C. 103(a) as being unpatentable over WO 00/73452 A2 (Ashkenazi et al, 2000), in view of WO 1994/22466 A1 (Cox et al, 1994, IDS filed February 2, 2006), Francis et al (Int. J. Hem., 68:1-18, 1998, IDS filed 2/2/2006), Byun et al (J. End., 169:135-143, 2001, IDS filed 2/2/2006) and Veronese et al (Biomaterials, 22:405-417, 2001, IDS filed February 2, 2006) as evidenced by Mondardini et al (Bioconj Chem, 6:62-69, 1995)[1], is maintained.

Claims 22-24 are herein drawn to conjugates comprising a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and one branched poly(ethylene glycol) group, said poly(ethylene glycol) group having an overall molecular weight of about 40 kDa and a composition comprising such a conjugate and a pharmaceutically acceptable carrier. Claim 22 further recites that the poly(ethylene glycol) (PEG) groups are linked to cysteine 110 and/or cysteine 117 of the polypeptide consisting of the amino acid sequence of SEQ ID NO:2[2].

Starting at page 3 of the response filed December 11, 2009, Applicant has

[1](see entire document, e.g., page 65, right column) The Mondardini et al reference is cited by Veronese et al at page 408 and evidences that Veronese et al teach methods of PEGylating proteins with a branched PEG group of about 40 kDa.

traversed this ground of rejection.

In this response, Applicant appears to argue that the instant claims are non-obvious because a conjugate species consisting of an IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated at cysteine 110 or cysteine 117 to a single branched poly(ethylene glycol) group of about 40 kDa has superior properties not shown in the prior art as compared to a conjugate species consisting of an IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to a linear poly(ethylene glycol) group of about 20 kDa. Applicant further appears to argue that because the specification sets forth data that this species of IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to branched poly(ethylene glycol) group of about 40 kDa has different and more desirable properties as compared to a conjugate species consisting of an IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to a linear poly(ethylene glycol) group of about 20 kDa and as compared to a IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 that there is evidence in the specification that establishes that the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to branched poly(ethylene glycol) group of about 40 kDa has unexpected properties which renders the claimed subject matter non-obvious.

In response, this argument is not found persuasive because while it is noted that the specification establishes that the different conjugates and unconjugated polypeptide have different properties, the argument that the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated at cysteine 110 or cysteine 117 to a single branched poly(ethylene glycol) group of about 40 kDa has unexpected properties is only supported by arguments of counsel and as previously set forth arguments of counsel cannot take the place of evidence in the record. As set forth in MPEP 716.01:

> Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of ***unexpected results***, commercial success,

[2] Such subject matter was previously encompassed by canceled claims 18-21 which were rejected over these references

> solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must. be established by factual evidence." See also In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); Ex parte George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991). The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal arguments.

Accordingly, while the arguments of counsel that the claimed conjugates produce unexpected properties are noted, they were not found persuasive as no affidavit or declaration include statements regarding unexpected results has been submitted to reasonably establish the non-obviousness of the claimed conjugates. Furthermore, it is noted that the properties being referred to in the response only pertain to the properties of species of conjugate consisting of an IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to a single branched poly(ethylene glycol) group of about 40 kDa wherein the polypeptide is PEGylated as cysteine 110 or cysteine 117, while the pending the encompass conjugates that are PEGylated at other sites or are PEGylated at both cysteine 110 and cysteine 117 and no evidence or scientific reasoning has been presented to establish that any of the properties of the conjugate species taught would be shared by the other conjugate species broadly encompassed by the claims.

Furthermore, as set forth in MPEP 716.02:

> Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (differences in sedative and anticholinergic effects between prior art and claimed antidepressants were not unexpected).

In this case, and as set forth previously, Veronese et al teach that branched PEG groups have multiple advantages over linear PEG groups, including higher retention in blood, lower immunogenicity and decreased inactivation of the proteins activity (See page 408, Figure 5 and page 412, Figure 14). Accordingly, based on the evidence of

record, it is submitted that the desirable properties of the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to a single branched poly(ethylene glycol) group of about 40 kDa wherein the polypeptide is PEGylated at cysteine 110 or cysteine 117 discovered in the instant application would be entirely expected by one of skill in the art since higher retention in blood, lower immunogenicity and decreased inactivation of the IGFBP-4 polypeptide would be expected to increase the efficacy of an IGFBP-4-PEG2 conjugate for inhibiting tumor growth and also lower the toxicity of such a conjugate due to its expected lower immunogenicity. Notably, Applicant has not supplied any evidence or affidavit which establishes that the properties of the disclosed IGFBP-4-PEG2 conjugate are anything other than what would be expected.

Additionally, in response to applicant's additional argument that the claims need not recite the properties of the disclosed conjugate, if the claims were commensurate in scope with the disclosed conjugate that displays such properties then the Examiner would agree. However, as set forth above, the pending claims encompass conjugates that are PEGylated at other sites or are PEGylated at both cysteine 110 and cysteine 117. Accordingly, it is apparent that the results presented are not commensurate in scope with the claimed invention and there is no evidence that the compounds encompassed by the claims would have similar properties to those compounds tested. For these reasons as well, Applicant's arguments relating to unexpected results are not found persuasive.

Finally, Applicant argues that the branched poly(ethylene glycol) group of about 40 kDa of Veronese has been treated to be an amine-specific reagent and that one of skill would not attach such a reagent to cysteine residues.

In response, it has not been submitted that an amine-specific reagent should be attached to cysteine residues. As set forth previously, considering the references as a whole, which teach methods and reasons for attaching poly(ethylene glycol) groups to cysteines, i.e., free thiol groups, of a IGFBP-4 polypeptide (see teachings of Ashkenazi et al, Cox et al, Francis et al and Byun et al) and the advantages of conjugating branched poly(ethylene glycol) group of about 40 kDa to polypeptides (see teachings of

Veronese et al), it is maintained that one of skill in the art would have been motivated to PEGylate the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 with a branched poly(ethylene glycol) group of about 40 kDa by partially reducing disulfide bonds to create free thiol groups at cysteine thiol residues 110 or 117 in the polypeptide and then conjugate a thiol-specific branched poly(ethylene glycol) group consisting of the amino acid sequence of SEQ ID NO:2 to the polypeptide. Notably, both Francis et al and Veronese et al teach methods of creating thiol-specific poly(ethylene glycol) groups for attaching to free thiol groups, so based on consideration of the references as a whole, one of ordinary skill in the art would have been motivated to make a conjugate of the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and a branched poly(ethylene glycol) group of about 40 kDa. Furthermore, since it was common to attach poly(ethylene glycol) groups to free thiol groups in polypeptides and the methods of preparing such reagents were known in the art as evidenced by Francis et al and Veronese et al, one of skill in the art also would have had a reasonable expectation of success in making a IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and a branched poly(ethylene glycol) group of about 40 kDa.

For these reasons and as further explained in the previous Office actions, as well as after careful and complete consideration of Applicant's response, this rejection is being maintained.

Conclusion

7. No claims are allowed.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and all claims could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS**

ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 5,932,462 (Harris et al, 1999, IDS filed 2/2/06) teaches branched PEG polymers for conjugating to polypeptides. EP 473,084 (Sumitomo, 1992, IDS filed 2/2/06) teaches branched PEG polymers for conjugating to polypeptides. (Shimasaki et al, 1999, of record) US Patent No. 6,004,775 (Shimasaki et al, 1999, of record) teaches a polypeptide that is 100% identical to SEQ ID NO: 2. US 2002/0177227 A1 (Kraus et al, 2002, of record) teach a polypeptide that is 100% identical to SEQ ID NO:2 and conjugating the polypeptides of the invention with polyethylene glycol. US Patent No. 5,212,074 (Kiefer et al, 1993, of record) teaches a polypeptide that is 100% identical to SEQ ID NO: 2. Damon et al (Endocrinology,139:3456-3464, 1998, IDS filed February 2, 2006) teach increasing serum levels of IGFBP4 *in vivo* in a mouse prostate cancer xenograft model delays prostate tumor formation. Miyakoshi et al (Endocrinology, 142(8)3456-3464, IDS filed 02/02/2006) teach an insulin-like growth factor binding protein 4 that increases IGF bioavailability in vivo. Reddy et al (ADDR, 54:571-586, 2002, of record), teach that it is routine to optimize the PEG polymer conjugated to a polypeptide based on size and type of polymer. US Patent No. 6,207,640 (Attie et al, 2001, of record) teach methods

of conjugating the proteins GH and/or IGF-I at one or two cysteine residues with monomethyl-PEG of between about 5000 Daltons to about 40000 Daltons to improve the circulating half-like for these proteins and administering such IGF-I conjugates with a IGFBP-4 polypeptide (e.g., column 13).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
January 6, 2010